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The 2019 European guidelines on pulmonary embolism illustrated with the aid of an exemplary case report

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Abstract: Background The European Society of Cardiology guidelines for the diagnosis and management of acute pulmonary embolism (PE) developed in collaboration with the European Respiratory Society (ERS) has been updated in 2019. Recommendations were added or updated on all stages of the evaluation and management of pulmonary embolism, encompassing diagnosis, early treatment, and long-term management. Case summary We illustrate an exemplary case, assembled for the purposes of this review, of a 70-year-old woman who presented at the emergency department with dyspnoea and thoracic pain. She was diagnosed with intermediate-high-risk acute PE and promptly treated with low molecular weight heparin. After 24 h of stay in intensive care unit, she was transferred to the cardiology department and switched to non-vitamin K-dependent oral anticoagulant apixaban 10 mg b.i.d. for 7 days and then 5 mg b.i.d. After discharge from the hospital 8 days later, she received standard-dose apixaban 5 mg b.i.d. for 6 months; the dose was reduced to 2.5 mg b.i.d. for long-term secondary prevention. During follow-up, investigations for PE sequelae were performed due to persisting dyspnoea. Discussion This exemplary case report puts into context the main novel recommendations from the 2019 ESC Guidelines, including the combination of clinical (pre-test) probability and adjusted D-dimer cut-offs for diagnosis of acute PE, the key role of right ventricular dysfunction in risk stratification, the choice and dosage of oral anticoagulant agents in early and extended anticoagulation, and the identification and management of chronic sequelae in the long-term follow-up.

DOI: <https://doi.org/10.1093/ehjcr/ytaa542>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-206723>

Journal Article

Published Version



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Originally published at:

Gallo, Andrea; Valerio, Luca; Barco, Stefano (2021). The 2019 European guidelines on pulmonary embolism illustrated with the aid of an exemplary case report. *European Heart Journal. Case Reports*, 5(2):ytaa542.

DOI: <https://doi.org/10.1093/ehjcr/ytaa542>

The 2019 European guidelines on pulmonary embolism illustrated with the aid of an exemplary case report

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Received 28 June 2020; first decision 2 September 2020; accepted 4 December 2020

Background

The European Society of Cardiology guidelines for the diagnosis and management of acute pulmonary embolism (PE) developed in collaboration with the European Respiratory Society (ERS) has been updated in 2019. Recommendations were added or updated on all stages of the evaluation and management of pulmonary embolism, encompassing diagnosis, early treatment, and long-term management.

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This exemplary case report puts into context the main novel recommendations from the 2019 ESC Guidelines, including the combination of clinical (pre-test) probability and adjusted D-dimer cut-offs for diagnosis of acute PE, the key role of right ventricular dysfunction in risk stratification, the choice and dosage of oral anticoagulant agents in early and extended anticoagulation, and the identification and management of chronic sequelae in the long-term follow-up.

Keywords

Pulmonary embolism • Guidelines • Venous thromboembolism • Anticoagulation • Case report

Learning points

- The diagnosis of acute pulmonary embolism (PE) is based on the combination of clinical pre-test probability, D-dimer levels, and imaging tests.
- The assessment of right ventricular function is key in risk stratification of patients with acute PE.
- Non-vitamin-K-dependent oral anticoagulants (NOACs) became the drug of choice for the early and the extended anticoagulant treatment in most patients with PE.
- Post-PE care and long-term follow-up represent a crucial part of PE management.

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Handling Editor: Tom De Potter

Peer-reviewers: Dmitry Duplyakov and Dan Octavian Nistor

Compliance Editor: Alexander Tindale

Supplementary Material Editor: Deepti Ranganathan

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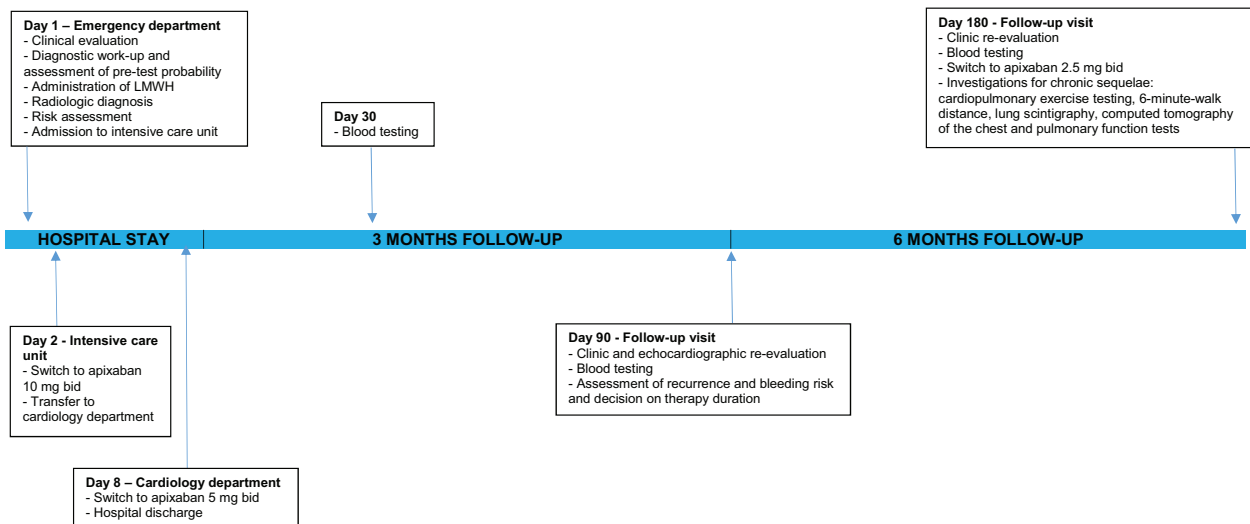
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Introduction

In 2019, the European Society of Cardiology (ESC), developed with the endorsement of the European Respiratory Society (ERS), published the new guidelines for the diagnosis and management of acute pulmonary embolism (PE)¹ updating the previous version from 2014.²

In this article, we present an exemplary case of acute PE with the aim of putting into context and discussing some of the novel recommendations concerning PE management from the 2019 ESC Guidelines. The updates most likely to affect clinical practice include the combination of clinical (pre-test) probability and adjusted D-dimer cut-offs for diagnosis, the role of right ventricular dysfunction in risk stratification, the choice and dosage of oral anticoagulant agents in early and extended anticoagulation, and the identification and management of chronic sequelae in the long-term follow-up. The readers will follow the case as it unfolds with each clinical decision accompanied by a discussion of the recommendations supporting it.

Timeline



Case presentation

A 70-year-old non-smoker Caucasian woman with arterial hypertension presented with a two-day history of dyspnoea and thoracic pain. Her blood pressure was 130/65 mmHg; heart rate was 112 beats per minute; peripheral oxygen saturation was 98% on room air and the respiratory frequency was 36/min. The remainder of her physical examination was normal, including soft, non-tender calves; her body weight was 75 kg. She described the chest pain as moderate and exacerbated by deep breathing. Dyspnoea was present at

rest at the time of evaluation. Two weeks before, she had suffered an ankle sprain that required bed rest with bathroom privileges for a few days. The patient denied any previous personal or family history of venous thromboembolic (VTE) events or any additional risk factors for VTE.

Routine tests included electrocardiogram (sinus tachycardia with negative T waves V2-V4), chest X-ray (normal findings), arterial blood gas (pO₂ 59 mmHg, pCO₂ 32 mmHg, normal pH and bicarbonate level). High-sensitivity troponin T was 52 ng/mL (normal range: <14 ng/mL) and NT-proBNP was 610 pg/mL (normal reference range <100 pg/dL).

The physicians at the Emergency Department calculated the Wells score, which was 3 (1.5 points for immobilization and 1.5 for tachycardia), indicating an intermediate pre-test probability of PE. Therefore, a D-dimer test was performed that returned a level of 1060 ng/mL (normal reference range <500 ng/mL). Administration of low-molecular-weight heparin (LMWH) at therapeutic dose was promptly started.

The diagnostic workup of PE without haemodynamic instability begins with the assessment of the patient's clinical (pre-test) probability of PE, which encompasses a combination of clinical findings and the evaluation of predisposing factors for venous thromboembolism (VTE). The Wells and the Geneva score, or their simplified versions, are simple and extensively validated prediction rules to assess the patient's probability of having acute PE.^{3,4} Specifically, the Wells score includes seven items regarding clinical history, symptoms, and signs suggestive of deep vein thrombosis (DVT) or PE. The 2019 ESC Guidelines endorse their use with a recommendation Class I and a level of evidence B (I, B). Their assessment serves to (i) initiate anticoagulation without any delay in patients with high or intermediate clinical probability of PE (I, C); (ii) perform an imaging test in patients with a high or intermediate clinical probability of PE; (iii) test D-dimer

levels in patients with a low clinical probability, in order to decide whether to perform computed tomography pulmonary angiography (CTPA) or a ventilation-perfusion (V/Q) lung scan.

In case of low or intermediate clinical probability of PE, guidelines recommend plasma D-dimer measurement (I, A). In contrast, D-dimer testing is not recommended in patients with high clinical probability of PE as a normal test does not safely exclude PE (III, A) and, therefore, a CTPA or a V/Q lung scan should be done without delay.

As the D-Dimer was above the age-adjusted cut-off of 700 ng/nL (for a patient aged 70 years), the physicians decided to perform an urgent CTPA. The CTPA showed multiple bilateral segmental pulmonary emboli and right ventricle enlargement.

A novelty of the 2019 ESC guidelines is the introduction of two alternatives (both rated as IIa, B) to a fixed D-dimer cut-off with the aim of increasing the specificity of D-dimer testing without affecting its sensitivity, thus reducing the number of patients unnecessarily undergoing CTPA. The first alternative is an age-adjusted D-dimer cut-off (age \times 10 mg/L, in patients aged >50 years), the second is the YEARS decision rule, which adapts the D-dimer cut-off measured at the time of clinical assessment to the clinical probability as assessed by a simplified Wells score with only three items.^{5,6}

Computed tomography pulmonary angiography is the imaging method of choice in patients with suspected PE.⁷ Pre-test clinical probability heavily influences both its negative and its positive predictive value. Accordingly, guidelines recommend rejecting the diagnosis PE if CTPA is normal in patients with a low or intermediate clinical probability of PE (I, A), accepting the diagnosis of PE if CTPA is positive in patients with an intermediate or high clinical probability (I, B).

The possibility of findings supporting alternative diagnoses is an advantage of CTPA over other imaging modalities. However, a study on patients undergoing CTPA for suspected PE found that findings supporting an alternative diagnosis only rarely had therapeutic consequences.⁸ Therefore, physicians should be aware that an inappropriate use of CTPA without a solid diagnostic work-up may have a limited value in the global management of the patient.

The echocardiogram confirmed right ventricle enlargement (RV/LV: 1.1 with a normal range considered to be below 1.0) with increased systolic pulmonary arterial hypertension (PAPs: 42 mmHg), decreased tricuspid systolic velocity (TAPSE; 14 mm) and decreased tricuspid annular peak systolic (S') velocity (<9.5 cm/s) on tissue Doppler imaging; McConnell's sign was absent while the 60/60 sign was positive. The patient was admitted to the intensive care unit (ICU) for 24-hour monitoring.

Diagnosis of PE must be accompanied by risk stratification: the risk categories are high risk, intermediate risk (further distinguished into intermediate-low and intermediate-high risk), and low risk.

Haemodynamic instability, defined as the presence of cardiac arrest, obstructive shock, or persistent hypotension, identifies high-risk patients, which must be monitored in an intensive care unit.

In patients without haemodynamic instability, further stratification into intermediate or low-risk categories is recommended by the guidelines as a next step (I, B) based on clinical prediction rules such as the Pulmonary Embolism Severity Index (PESI) or its simplified version (sPESI; IIa, B). Overall, a PESI of Class I–II is a reliable predictor of low-risk PE. Echocardiography or CTPA can identify signs of right ventricular (RV) dysfunction the findings most frequently associated with unfavourable prognosis include a right ventricular/left ventricular diameter ratio (RV/LV) ≥ 1.0 and a TAPSE < 16 mm.^{9,10} Plasma levels of troponin and N-terminal (NT)-proBNP are markers of myocardial injury and RV pressure overload, respectively.^{11,12} Patients in the intermediate-risk group who display evidence of both RV dysfunction on imaging and elevated cardiac biomarker levels are classified into the intermediate–high-risk category. These patients should be monitored in an intensive care unit to permit the early detection of haemodynamic decompensation or collapse, so that appropriate measures can be taken promptly (I, B). Conversely, patients with no signs of RV dysfunction and/or normal cardiac biomarker levels belong to the intermediate–low-risk category; these patients do not require monitoring in an intensive care unit but should be hospitalized.

Selected patients with low-risk PE should be considered for early discharge and home anticoagulant treatment. Purely clinical assessment tools, such as the PESI, evaluate PE-related complications or comorbidities. Tools such as the Hestia exclusion criteria also include the patient's expected compliance, family, and social environment, as well as the local coordination between primary and secondary care. The recommendation of home treatment for selected patients remains unchanged from the 2014 ESC guidelines, but its grade was increased on account of the results of the international investigator-initiated Home Treatment of patients with acute PE (HoT-PE) phase IV trial¹³ and of a meta-analysis of observational studies showing that in low-risk patients with acute PE classified based on clinical scores alone, the absence of RV dysfunction on admission on top of other clinical criteria was associated with a negligible rate of early PE-related complications and death.¹⁴ In line with this principle, the guidelines specify that assessment of RV function should be included in the risk stratification of all patients with acute PE if early discharge is considered.

During ICU stay, rescue thrombolytic therapy was not necessary. After transferral to the cardiology ward, she was switched to the non-vitamin K-dependent oral anticoagulant (NOAC) apixaban at a dosage of 10 mg twice daily, based on her body weight of 75 kg and an estimated glomerular filtration rate of 69 mL/min. A compression ultrasound of the lower limb excluded DVT.

The 2019 ESC guidelines confirm previous recommendations to reserve systemic thrombolytic therapy to high-risk patients (I, B). Surgical pulmonary embolectomy (I, C) or percutaneous catheter-directed treatment (IIa, C) are recommended if thrombolysis is contraindicated or has failed. In intermediate-risk patients, the clinical benefit of systemic thrombolysis is absent due to the substantial bleeding rate of this treatment strategy.¹⁵ Therefore, guidelines discourage routine use for these patients (III, B).

The specifications of the 2019 ESC Guidelines for the long-term management of PE reflect an understanding of PE as a chronic disease. Persisting dyspnoea may be one of the signs of chronic conditions directly related to the underlying thrombo-embolic disorder. Chronic thromboembolic pulmonary hypertension (CTEPH), a life-threatening condition being diagnosed in approximately 3% of PE survivors,²⁴ is associated with substantial morbidity and mortality and defined by a mean pulmonary arterial pressure of more than 25 mmHg with a pulmonary arterial wedge pressure of less than 15 mmHg, documented at right heart catheterization in a patient with mismatched perfusion defects on V/Q lung scan.²⁵ Post-PE impairment (PPEI) is an umbrella definition encompassing echocardiographic abnormalities pointing to the presence of pulmonary hypertension combined with a cardiopulmonary symptomatology.²⁶ Chronic thromboembolic disease (CTED) should be considered in symptomatic patients with documented post-thrombotic obstructions but normal pulmonary haemodynamic parameters at rest and without any other cause of their marked exercise limitation.²⁷

Accordingly, further diagnostic evaluation should be considered in patients with persistent or new-onset dyspnoea/exercise limitation after PE (IIa, C). In symptomatic patients with mismatched perfusion defects persisting on V/Q scan beyond 3 months after acute PE, referral to a PH/CTEPH expert centre is recommended, after taking into account the results of echocardiography, natriuretic peptide levels, and/or CPET (I, C).

Lead author biography



Stefano Barco completed his residency in internal medicine at the University of Pavia, Italy, and received a PhD in Vascular Medicine from the University of Amsterdam, the Netherlands. He leads a research group at the Center for Thrombosis and Hemostasis (Mainz, Germany) and is staff physician at the Clinic of Angiology, University Hospital Zurich, Switzerland. Dr Barco's research interests are in the manage-

ment of pulmonary embolism and rare thromboembolic disorders. He is involved as Steering Committee member of multinational trials in pulmonary embolism. He is associate editor for Thrombosis Research and Haemostaseologie-Progress in Haemostasis, and serves as a referee for several top journals in the field.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: This is an exemplary case, as such, patient consent is not required.

Conflict of interest: S.B. reports personal fees from Bayer HealthCare, personal fees from BTG Pharmaceuticals, personal fees from LeoPharma, personal fees from Daiichi Sankyo, personal fees from Bayer HealthCare, outside the submitted work.

Funding: This work was not funded. The work of Andrea Gallo, Luca Valerio and Stefano Barco was supported by the German Federal Ministry of Education and Research [BMBF 01EO1003 and 01EO1503].

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